Result Page

The present invention is relative with the new derived ones from aryl-I (IH) quinazolone-4, like with the preparation and the pharmaceutical applying of these new drifts.

New derived, following the invention, are represented by formula I
EMI1.1
in which R1 represents a hydrogen atom or a radical alkyl, R2 represents a hydrogen atom or a radical methyl, R3 represents a radical methyl, trifluoromethyl, Nitro, chloro or fluoro and R4 a hydrogen atom or a radical alkyl, hydroxy, alkoxy, acyloxy, chloro, fluoro, trifluoromethyl or Nitro
Radical R2, R3, and R4 can be grafted on the corresponding nucleuses in the different possible positions.

By radical alkyl, one understands a soldering iron carbonaceous, linear or ramified from 1 to 4 carbon atoms.

Radical the alkoxy and acyloxy are defined of identical manner.

The invention also refers to the made up new salts these obtained by acid addition the pharmaceutically acceptable ones, for example of mineral acids like chloride and bromide of hydrogen, the sulfuric acid, the phosphoric acid or of organic acids, like the acids lactic, tartaric, acetic, salicylic, citric, benzoic.

As regards composed of the present invention, when R1 and R4 represent simultaneously hydrogen, one will note, for this purpose, that the publication of S. Somase will khara and have. (Current Sciences 33, 1964, 521) cannot constitute a valid anteriority. Indeed, the structure of the synthesized products such as it is represented in this publication does not correspond by no means to that described by the authors, since it is not a question of aryl-I (IH) quinazolones-4 but else of aryl-I tétrahydro-1,2,3,4 quinazolones-4 answering the following formula
EMI2.1

As one will be able to note it, the derivatives of Somasekhara et al. are in fact of the tétrahydrogénés derivatives and not of the derivatives dihydrogénés like the derivatives of the invention answering formula I.

This fact was supported by work of Chatterjee A (J.Indian Chem. Ploughshare 46, 1969, 103, 104) and of Irwin W.J. (J.Chem. Ploughshare Trans Perkin. 1, 1972, 353) front to be put in evidence by the applicant.

The results of this work show that the process of Somasekhara or Mukherjee and Al, which consists in making react anthranilic acids with formamide under conditions of temperature, pressure and duration determined, does not make it possible to obtain aryl-I (IH) quinazolones-4, such as the product (I) represented with page 104 of the article of
Chatterjee and Al but many aryl-I tétrahydro-1,2,3,4 quinazolones-4 such as the product (III) represented with the même page of this same article. The analyses of spectometry of mass, of nuclear and infra-red magnetic resonance indeed make it possible to establish that the molecular formulas of the products quoted in the article of Somasekhara are erroneous, the derivatives of Somasekhara indeed showing an intense infra-red absorptance band around 3100-3200 cm 1 characteristic of function N-H as well as a signal with T + 5 characteristic of the two protons in position 2 (- CH2 of the méthylènediamino group) of derived the t-piece trahydrogénés.

On the other hand, the corresponding dihydrogénés derivatives do not present infra-red absorptance around 3100-3200 cm (N-H) nor, in R.M.N., the corresponding signal with # # 5 with the two protons in 2 of the tétrahydrogénés derivatives but show, in R.M.N., with # T = + 3 a corresponding singlet with the single proton in position 2.

One will note also that although Somasekhara and Al mention in their article which products that they synthesized belong to a family of made up expressing generally properties bronchodilatatrices and sedative with the level of the muscles, they explicitly do not quote the pharmaceutical activities conferred by these products.

The new according compounds with the invention are prepared by treatment of the substances answering the general formula II: (see P.F. JUBY: J. Med. Chem. 11 (1968) 111, H, Mr. Blatter and Al J. Org. Chem. 30 (1965) 1020, A. Chatterjee and Al J. Ind. Chem. 46 (1969) 103, J.P. Osselaere with avoided tre)
EMI3.1
in which Ro, Ra and RA such as are described previously, that is to say by the ethyl orthoformate
EMI3.2
if is hydrogen, in presence or not of a dehydrating agent, that is to say by corresponding acid chloride, if R1 is a radical alkyl, in presence or not of a dehydrating agent.

One obtains, following the invention, the derivatives of the formula I in which R1 represents hydrogen, by treating the derivative of formula II for example, by ten times its weight of orthoformate, at the temperature of 1300C, pendent 48 hours, while periodically distilling formed ethanol during the reaction.

One can also proceed by treatment of 1 part of derived from formula II by 5 to 20 parts of a mixture (2/1) of orthoformate of ethyl and, as dehydrating agent, of acetic anhydride, in presence or not of a solvent generally considered as inert in this type of reaction, such as toluene for example, at a temperature ranging between 900C and that of the boiling of the mixture, pendent one period varying from 4 to 48 hours.

Another alternative of the invention consists in treating 1 mole of derived from general formula II by 5 to 10 times its weight of ethyl orthoformate, in presence, as dehydrating agent, of at least a mole of phosphorus oxychloride. One proceeds under agitation, at a temperature ranging between the ambient temperature and 1200C, the addition of oxychloride being gradual and agitation being still continued, at constant temperature, pendent 60 to 120 minutes after the addition of oxychloride. One also can, in this case, to proceed in the presence of a solvent which can be regarded as inert under the conditions of the reaction, such as, for example, benzene, toluene, xylene, etc... It will be noted also that one could use as dehydrating agent, in addition to the acetic anhydride and phosphorus oxychloride, of pyridine or a mixture of these different made up.

One prepares, following the invention, the derivatives of the formula I, in which R1 is a radical alkyl, while treating, for example, a mole of derived from formula II, dissolved in 10 parts of a mixture 1/1 of pyridine (dehydrating agent) and toluene (solvent), by 2 moles of pendent corresponding acid chloride 18 hours, under agitation, at a temperature corresponding with that of the boiling of the mixture.

It is clearly understood that dehydrating agents and other solvents than pyridine and toluene quoted above are appropriate also.

The according compounds with the invention can be purified by a suitable process, like crystallization, fractional distillation, the distribution with against current and the chromatography.

One gives hereafter a certain following number of examples of preparation of products the invention.

EXAMPLE 1 (Trifluoromethyl-3 phenyl) - I (1H) quinazolonc-4
Process A
A mixture of 5g from (trifluoromethyl-3 anilino) 2 benzamide and of 50ml of ethyl orthoformate is carried to boiling while heating with pendent backward flow 24 hours. At this time, one distils the half of the solution and, after distillation, one adds 25ml ethyl orthoformate One carries again to boiling while heating to pendent backward flow 24 hours.

The solution is then cooled and evaporated dry under reduced pressure. The residue is recristallized in a mixture (1/1) of benzene-pétroléine (EP. : 100-140 C). One obtains thus 3 G of (trifluoromethyl-3 phenyl) - L (IH) quinazolone-4. P.F. : 179 C.

Process B
A mixture of 5 G (trifluoromethyl-3 anilino) 2 benzamide, of 25 ml of orthoformate of ethyl, 12,5 ml of acetic anhydride and 90 ml of toluene is carried to boiling while heating with pendent backward flow 8 hours. After cooling, the solution is evaporated dry under reduced pressure. The residue, taken again by 50 ml of pétroléine (EP. : 500-750C), is brought on filter, is dried and recristallized in a mixture (1/1) of benzene and pétroléine (EP. : 100-140OC) One obtains 5 G from (trifluoromethyl-3 phenyl) -1 (IH) quinazolone-4. P.F. 1790C.

Process C
In a balloon with 3 pipes, provided with a magnetic agitator, a cooling agent and a bulb, one places 7 G of (trifluoromethyl-3 anilino) - 2 benzamide and 50ml of ethyl orthoformate the mixture are carried, under agitation, at the temperature of 90-950C and are maintained pendent IO minutes at this temperature. One then adds drop by drop a solution of 3,85 G phosphorus oxychloride in 20 ml of toluene. After complete addition, the agitated solution still is heated with 950C pendent 60 minutes. The cooled solution is then evaporated dry, under reduced pressure. The residue is taken again by water (50-60ml), the pH of the aqueous phase is brought to 8-9 per addition of soda bicarbonate. One then extracts three times by 50 ml from chloroform. The chloroformic extracts joined together, dried on calcic chloride, are filtered and evaporated dry under reduced pressure. (Trifluoromethyl-3 phenyl) the 1 (1H) quinazolone-4 is recristallized in a mixture (1/1) of benzene and pétroléine (EP. : 100-140 C). Pendement: 75%.

P.F. : 179 C.

Elemental analysis: C15H9N2OF3
% calculated: C: 62,06%; H: 3,10 % ; NR: 9,66 %
% found: C: 61,88%; H: 3,22 % ; NR: 9,81 %
EXAMPLE 2
Ethyl-2 (trifluoromethyl-3 phenyl) - 1 (1H) quinazolone-4
Into a balloon with three pipes, provided with a cooling agent, a mechanical agitator and a bulb, one introduces 5,6 G of (trifluoromethyl-3 anilino) - 2 benzamide, 50 ml of pyridine and 50 ml of toluene. One agitates until dissolution then one adds, drop by drop, under agitation, a solution of 3,7 G propionyl chloride in 20 semi of toluene. The mixture is then carried to boiling while heating has backward flow, under agitation, pendent 18 hours. After refroidisserent, one evaporates dry under reduced pressure. The residue is taken again by 50-60 ml of water and the pH of the aqueous phase is checked and adjusted, with the need, the value of 9-10 per sodic addition of carbonate
The aqueous phase is then extracted by 3 times 50 ml from chloroform. The chloroformic extracts joined together dried on chlo- calcic rure, are filtered and evaporated dry under reduced pressure
The residue, made up of ethyl-2 (trifluoromethyl-3 phenyl) - 1 (1H) quinazolone-4, is recristallized in a mixture (1/1) of benzene and pétroléine (EP. : 50-750C). Output: 60-70 X.

P.F. : 1820C.

Elemental analysis: C17H13N2OF3
% Calculated: C: 64,15%, H: 4,09 % ; NR: 8,81% % Found: C: 64,37% ; H: 4,15 % ; NR: 9,00 %
EXAMPLE 3
Chloro-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the processes B and C of example 1. Recrystallization: benzene-pétroléine (100-140 C). P.F 1980C.

Elemental analysis: C14H9N2OCl
% Calculated: C: 65,49%; H: 3,50%, NR: 10,92 %
% Found: C: 65,33%; H: 3,51 % ; NR: 10,99 %.

EXAMPLE 4 (Chloro-4 Phenyl) - L (IH) quinazolone-4
Obtained following the processes B and C of Rexem- ple 1. Recrystallization: benzene-pétroléine (100-140 C). P.F.

2130C.

Elemental analysis: C14H9N2OCl
% Calculated: C: 65,49%; H: 3,50 % ; NR: 10,92 %
% Found: C: 65,27%; H: 3,65 % ; NR: 11,04 %
EXAMPLE 5 (Nitro-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the process B of example 1.

Recrystallization: pyridine-pétroléine. (EP. : 100-140 C).

P.F. : 275,50C.

Elemental analysis: C14H9N3 0 3
% Calculated: C: 62,92%; H: 3,37 % ; NR: 15,73 %
% Found T C: 63,13%; H: 3,53 % ; NR: 15,81 %
EXAMPLE 6 (Fluoro-4 phenyl) - L (IH) quinazolone-4
Obtained following the process B of example 1. Recrystallization: benzene-pétroléine (EP. : .100-140 C).

: 237,5 C.

Elemental analysis: C14HgN20F
% Calculated: C: 70,00%; H: 3,75 % ; NR: 11,67 %

% Found: C: 69,83%; H: 3,91 % ; NR: 11,81 %
EXAMPLE 7 (Methyl-2 chloro-3 phenyl) - L (1H) quinazolone-4
Obtained following the process B of example 1. Recrystallization: benzene-pétroléine (EP. : 100-140 C).

P.F. : 1700C.

Elemental analysis: C15H11N2OC1
% Calculated: C: 66,54 ; H: 4,07 ; NR: 10,35
% Found: C: 66,37 ; H: 4,12 ; NR: 10,49
EXAMPLE 8
Methoxy-6 (trifluoromethyl-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the processes B and C of example 1 Recrystallization: benzene-pétroléine (EP. : 100-140 C).

P.F. : 2180C.

Elemental analysis: C16H11N2O2F3
% Calculated: C: 60,00 ; H; 3,43 ; NR: 8,75
% Perforates: C: 59,94 ; H: 3,58 ; NR: 8,88
EXAMPLE 9 (Chloro-3 phenyl) - 1 methoxy-6 (1H) quinazolone-4
Obtained following the process B of example 1.

Recrystallization: benzene-pétroléine (P.E, 100-140 C).

P.F. : 168,50C.

Elemental analysis: C15H11N2O2Cl
% Calculated: C: 62,83 ; H: 3,84 ; NR: 9,77
% Found: C: 62,63 ; H: 3,93 ; NR: 9,83
EXAMPLE 10 (Chloro-4 phenyl) - L methoxy-6 (1H) quinazolone-4
Obtained following the processes B and C of example 1. Recrystallization: benzene-pétroléine (EP. : 100-140C).

P.F. : 143,50C.

Elemental analysis: C15H11N2O2C1
% Calculated: C: 62,83 ; H: 3,84 ; NR: 9,77
% Found: C: 62,76 ; H: 4,01 ; NR: 9,87
EXAMPLE 11
Chloro-7 (chloro-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the process B of example 1.

Recrystallization: benzene-pétroléine (EP. 100-140 C)
P.F. : 1950C.

Elemental analysis: C14H8N2OCl2
% Calculated: C: 57,73 ; H: 2,75 ; NR: 9,62
% Found: C: 57,64 ; H H: 2,69 ; NR: 9,77
EXAMPLE 12
Chloro-7 (trifluoromethyl-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the process B of example 1.

Recrystallization: benzene-pétroléine (EP. 100-140 C).

P.F. : 195,50C.

Elemental analysis: C15H8N2OF3C1
% Calculated: C: 55,47 ; H: 2,47 ; NR: 8,63
% Found: C; 55,61 ; H: 2,44 ; NR: 8,81
EXAMPLE 13
Chloro-6 (chloro-3 phenyl) - 1 (1H) quinazolone-4
Obtained following the process B of example 1.

Recrystallization: benzene-pétroléine (EP. 100-140 C).

P.F. : 2000C.

Elemental analysis: C14H8N2OCl2
% Calculated: C: 57,73 ; H: 2,75 ; NR: 9,62
% Found: C: 57,94 ; H: 2,80 ; NR: 9,69
EXAMPLE 14 (Chloro-3 phenyl) - 1 ethyl-2 (1H) quinazolone-4
Obtained following the process of example 2.

Recrystallization T benzene-pétroléine (P.E 100-140 C).

P.F. : 2480C.

Elemental analysis T C16H13N2OC1
% Calculated: C: 67,49 ; H: 4,57 ; NR: 9,84
% Found: C: 67,42 ; H: 4,55 ; NR: 9,96
EXAMPLE 15 (Chloro-4 phenyl) - 1 ethyl-2 (1H) quinazolone-4
Obtained following the process of example 2.

Recrystallization: benzene-pétroléine (EP. 100-140 C).

P.F: 2060C.

Elemental analysis: C16H13N2OCl
% Calculated: C: 67,49 ; H T 4,57; NR: 9,84
% Found: C: 67,68 ; H: 4,80 ; NR: 9,97
EXAMPLE 16 (Chloro-3 methyl-2 phenyl) - L ethyl-2 (1H) quinazolone-4
Obtained following the process of example 2,
Recrystallization: pétroléine 100-140 C. P.F. : 121 C.

Elemental analysis: C17H15N2OCl
% Calculated: C 68,3; H: 5,02 ; NR: 9,38
% Found: C 68,41; H: 4,79 ; NR; 9,61
EXAMPLE 17 (Chloro-3 phenyl) - L ethyl-2 methoxy-6 (1H) quinazolone-4
Obtained following the process of example 2.

Recrystallization: benzene-pétroléine. (EP. 100-140 C).

P.F. : 193 C.

Elemental analysis: C17Hl5N202Cl
% Calculated: C: 64,86 ; H H: 4,77 ; NR: 8,90
% Found: C Z 64,93; H Z 4,83; NR Z 9,01
The acute toxicity of the substances following it in wind ion was studied on female mice of homogeneous race NMRI while determining, according to the method of Karber and Behrens, the lethal amount for 50% of the animals over one 7 days period after the intraperitoneal injection of different amounts of the substan- these. The results are expressed in milligrams of substance/kg of bodily weight (Table I) One will note that the acute toxicity of the substances is generally relatively low.

TABLE I
Substance of DL50 (Mg/kg - I.P.) the Example NR 1 ..... 267 2 200
3 ..... 200 4 ..... 234 5 550 6, 200 7 434
8 ..... > 550 9 ..... 200 10 ..... 200 L 300
12 ..... > 450 13 ..... 100 14 ..... 200 15.200
16 .....> 550 17 200
The synthesized substances were also managed with animals (mouse, rats) in order to put in evidence and to study by means of specific tests various pharmacological effects.

Certain substances, for example those of examples 1, 3, 4, 8, 10, 11 and 15, have effects of the type hypnosédetif or tranquillizing. These substances involved, in the rat and the mouse, of the disturbances of the reflex of rectification, energy of the deceleration until complete abolition according to amounts', managed by gastric, and pendent way of variable times according to substances'. There is also desired an antagonistic effect of these substances with respect to an amount of cardiazol involving a mortality of 100% in the mouse (100 Mg/kg per intra-peritoneal way). The substance of example 1 has protected 50% of the animals to the amount of 40 Mg/kg., that of example 4 with the amount of 62 mg/kg and that of example 3 with the amount of 47 mg/kg (substances managed by gastric way In the same conditions, one obtained a same percentage of protection with an amount of sécobarbital of 10 mg/kg, with an amount of méthaqualone of 30 mg/kg and with an amount of méprobamate of 70 mg/kg.

Into therapeutic, some of the synthesized substances could thus be used for their action on the central nervous system and, especially like hypno-sedatives or tranquillizing.

The diuretic action of the synthesized substances was also studied in the rat. Pendent the 24 hours which follow the administration of the substances by gastric way, one measuring volumes of the emitted urines and one compares the values found with those supplied, on the one hand, by pilot animals, and, on the other hand, by animals treated by triamterene chosen like substance of reference. The substance of the example 14 increased by 2,26 times the volume of the diuresis to the amount of 10 mg/kg, the substance of example 1 of 2,4 times at the amount of 2,5 mg/kg and triamterene of 2,35 times at the amount of 10 mg/kg.

Into therapeutic, some of the synthesized substances could thus be used for their diuretic effect.

Several of the synthesized substances also showed an activity anti-inflammatory drug in the oe- dème with the carrageenan of the leg of the rat according to the technical one of Winter (Winter, Risley and Nuss - Proc Soc. exp. Biol. Puts., 111, 544, 1962). The measuring of enflure of the legs was carried out by means of the plethysmometer of Lenca; the optional reduction of the oedeme was calculeepar report/ratio with rats pilot and compared with those obtained by means of the diphénylbutazone, of the acid niflumic and the acetyl-salicylic acid chosen like substances of reference - (Table II).

TABLE It
Oedema with the carraénine
Substance of Amount of substance the Example NR giving a réduc
tion of 50% of
oedema 1 ..... 135 3 ..... 60 4.240 9.126 10.125 11 95
13 ..... 100 14 ..... 22 15 120
Phenylbutazone ..... 137 AC. niflumic 135
Ac. acetyl-salicylic 160
The amounts are expressed out of Mg per kg and the substances are managed by gastric way.

Some of the synthesized substances are thus endowed with an activity anti-inflammatory drug susceptible to be used into therapeutic, for example in cases of rheumatic complaints.

This activity appears all the more interesting as, in the case of the substances of which the ulcerogenic effect already was studied, this effect proves clearly low with that of the substances of reference, even null under the test conditions (Table III).

TABLE III
Substance of Index of ulcéral' Example NR tion and amounts
corresponding 1 ..... 0,12 to 200 mg/kg 4,... with with 200 mg/kg 3 0 to 200 mg/kg
TABLE III (Continuation)
Substance of Index of ulcéral' Example NR tion and amounts
corresponding 5 ..... 0 to 200 mg/kg 14 0 to 200 mg/kg 11. 0 to 200 mg/kg
12 ..... 0,08 to 100 mg/kg
Phenylbutazone ..... 0,04 to 50 mg/kg
..... 1,15 to 100 mg/kg
..... 5,44 to 200 mg/kg
Ac. niflumic ..... 5,78 to 25 mg/kg
..... 12,00 12,00 to 50 mg/kg
..... 16,90 to 200 mg/kg
Ac. acetyl-salicylic ..... 0,20 to 25 mg/kg
..... 0,85 to 50 mg/kg
..... 15,80 to 100 mg/kg
This test of gastric ulceration is based on the technical one of Robert and Nezamis (Robert and Nezamis - Proc. Ploughshare

Exp. Biol. Med. 99, 443,1958). One uses male rats SPF, the substances are managed by gastric way. For the calculating of the index of ulceration one holds account at the same time total number of animals, percentage of ulcerous animals, number and gravity of the ulcerous injuries.

The action analgesic of the synthesized substances was also studied in the mouse according to technical based on the text of Siegmund to the para-phénylbenzoquinone (Siegmund, Cadmus and Lu - Proc. Ploughshare Exp. Biol. Med., 95, 729, 1957). One determines the amount of substance which, managed by intra-gastric way, entratne an analgesia of 50% (DF 50) compared to the pilot animals and one compares with the supplied results by the codeine, the phenylbutazone and the acid niflumic chosen like substances of reference. (Table IV).

TABLE IV
Substance of D.E. 50
The Example NR (mg/kg-I.G.) 1 27 4 26 3 12,5 8 82 7 31 5 4 9 85 10 ..... 48 17 55
14 ..... 30 15 35 2 90 L 43
Codeine (in base) 14
Phenylbutazone 45 ac. niflumic, 106
Some of the synthesized substances are thus endowed with an activity analgesic susceptible to be used into therapeutic in the purpose removing or attenuating acute or chronic painful feelings, various origaines
The present invention has also as an object of the pharmaceutical compositions which contain like active one or more compounds of general formula I, single components or with other active substances of similar or different effects, in mixture with a suitable pharmaceutical vehicle.

These pharmaceutical compositions can star solid like caked or coated tablets, with one or more layers, caplets, gélules, powders dispersible or soluble, suppositories, or liquid, as solutions, eye lotions, suspensions, emulsions, syrups, preparations intended for the parenteral administration, including the pulmonary or bronchial way, for example in the form of aerosol.

The solid compositions for the oral use can be prepared by mixing one or more according substances with the invention for example with milk sugar, caster sugar, starch, talc, with products intended to delay of them or to prolong the effects of them, for example cellulose the acétophtalate, the stearates of glyceryl, the exchanging resins of ions.

The suppositories can between prepared by incorporating one or more according substances in the invention with cocoa butter for example, have with very other suitable substance, like the mono ones, di- and triglycerides of saturated fatty acids.

The liquid compositions can be prepared for example by dissolution, bringing in suspension or emulsion, at the moment of the preperation or directly front the administration, of one or more according substances to the invention and into other of very other product whose presence is judged penny ha counts or necessary, such as for example, of the preservatives, such as the p-hydroxybenzoates of methyl and propyl, thickening and emulsifier like the cellulose derivatives and esters of polyoxyethylene sorbitane, of sweetening and flavouring as sugar, saccharin, the sorbitol, the natural or synthetic gasolines, of the isotonisants like sodic chloride or the plugs like sodic phosphates, in water distilled, in other liquid the hydroxylated acceptable ones such as ethanol, glycerin, certain glycols, in mixtures of these solvents or pharmaceutically acceptable oils.

Result Page

CLAIMS

1. Derived from aryl-1 (1H) quinazolone-4, caracté riséspar the fact that they answer the general formula:
EMI16.1
in which R1 represents a hydrogen atom or a radical alkyle, R2 represents a hydrogen atom or a radical methyl, R3 represents a radical methyl, trifluoromethyl, Nitro, chloro or fluoro and R4 a hydrogen atom or a radical alkyl, hydroxy, alkoxy, acyloxy, chloro, fluoro, trifluorométhy it or Nitro
2.Dérivés of aryl-1 (1H) quinazolone-4 following claim 1, characterize in that in formula I, when R1 represents a radical alkyl, this one linear or is ramified and includes/understands from 1 to 4 carbon atoms, and when R4 represents a radical alkyl, alkoxy or acyloxy, this one linear or is ramified and includes/understands from 1 to 4 carbon atoms.

3. Proceeded of preparation of derived from aryl-1 (1H) quinazolone-4, answering the formula I in which R1 represents Ehydrogene and R2, R3 and R4 has the given significances previously, characterized in that one does derived réagirjun answering the general formula
EMI16.2
in which R2, R3, R4 are such as defined previously, with ethyl orthoformate.

4 Method of preparation of derived from aryl-1 (1H) quinazolone-4 answering formula I, in which R1 is a radical alkyl and R2, R3 and R4 have the given significances previously, characterized in that one makes react a derivative answering the general formula:
EMI17.1
in which R1, R3 and R4 are such as defined previously, with corresponding acid chloride.

5 following Process one or the other one of the claims 3 and 4, characterized in that one carries out the reaction in the presence of a dehydrating agent.

6. Following process claim 5, characterized in that the dehydrating agent is selected in the formed group by acetic anhydride, phosphorus oxychloride, pyridine and the mixtures of these compounds.

7. Derivatives following one or the other one of the claims 1 and 2, characterized in that they are made up p of pharmaceutically acceptable salts of acid addition of the derivatives answering formula I
8. Pharmaceutical composition, characterized in that it includes/understands at least one of the compounds answering formula I, in which R1, R2, R3 and R4 have the given significance, or a salt of acid addition of this one, and one excipient suitable and optionally of other therapeutic agents.

9. Use of derived from formula I, their salts of acid addition and/or composition following claim 8, as agents having an activity nerve sedative, tranquillizing, diuretic, anti-inflammatory drug and/or analgesic, these derivatives or salts being used single or in COM binaison with excipients and/or other therapeutic agents having RUE similar or different activity.